

Effects of hyperoxia on ventilation and pulmonary hemodynamics during immersed prone exercise at 4.7 ATA: possible implications for immersion pulmonary edema

Dionne F. Peacher, Shelly R. H. Pecorella, John J. Freiberger, Michael J. Natoli, Eric A. Schinazi, P. Owen Doar, Albert E. Boso, Aaron J. Walker, Matthew Gill, Dawn Kernagis, Donna Uguccioni, and Richard E. Moon

Center for Hyperbaric Medicine and Environmental Physiology, Department of Anesthesiology, Duke University Medical Center, Durham, North Carolina

Submitted 23 December 2009; accepted in final form 22 April 2010

Peacher DF, Pecorella SR, Freiberger JJ, Natoli MJ, Schinazi EA, Doar PO, Boso AE, Walker AJ, Gill M, Kernagis D, Uguccioni D, Moon RE. Effects of hyperoxia on ventilation and pulmonary hemodynamics during immersed prone exercise at 4.7 ATA: possible implications for immersion pulmonary edema. *J Appl Physiol* 109: 68–78, 2010. First published April 29, 2010; doi:10.1152/jappphysiol.01431.2009.—Immersion pulmonary edema (IPE) can occur in otherwise healthy swimmers and divers, likely because of stress failure of pulmonary capillaries secondary to increased pulmonary vascular pressures. Prior studies have revealed progressive increase in ventilation [minute ventilation (\dot{V}_E)] during prolonged immersed exercise. We hypothesized that this increase occurs because of development of metabolic acidosis with concomitant rise in mean pulmonary artery pressure (MPAP) and that hyperoxia attenuates this increase. Ten subjects were studied at rest and during 16 min of exercise submerged at 1 atm absolute (ATA) breathing air and at 4.7 ATA in normoxia and hyperoxia [inspired P_{O_2} ($P_{I_{O_2}}$) 1.75 ATA]. \dot{V}_E increased from early (E, 6th minute) to late (L, 16th minute) exercise at 1 ATA (64.1 ± 8.6 to 71.7 ± 10.9 l/min BTPS; $P < 0.001$), with no change in arterial pH or P_{CO_2} . MPAP decreased from E to L at 1 ATA (26.7 ± 5.8 to 22.7 ± 5.2 mmHg; $P = 0.003$). \dot{V}_E and MPAP did not change from E to L at 4.7 ATA. Hyperoxia reduced \dot{V}_E (62.6 ± 10.5 to 53.1 ± 6.1 l/min BTPS; $P < 0.0001$) and MPAP (29.7 ± 7.4 to 25.1 ± 5.7 mmHg, $P = 0.002$). Variability in MPAP among subjects was wide (range 14.1–42.1 mmHg during surface and depth exercise). Alveolar-arterial P_{O_2} difference increased from E to L in normoxia, consistent with increased lung water. We conclude that increased \dot{V}_E at 1 ATA is not due to acidosis and is more consistent with respiratory muscle fatigue and that progressive pulmonary vascular hypertension does not occur during prolonged immersed exercise. Wide variation in MPAP among healthy subjects is consistent with variable individual susceptibility to IPE.

diving; blood gas analysis; pulmonary circulation; pulmonary wedge pressure

IMMERSION PULMONARY EDEMA (IPE) is a syndrome characterized by dyspnea, cough, expectoration of blood-tinged sputum, and hypoxemia, which can occur in otherwise healthy individuals during diving and surface swimming. Since the first description of IPE in 1989 by Wilmshurst et al. (67) in scuba divers in cold waters, there have been many reported cases (1, 6, 9, 20, 41).

Evidence from case reports and case series supports the notion that IPE represents a form of hemodynamic pulmonary edema (31, 39, 41, 67), probably due to the additive effects of

immersion-induced increase in pulmonary blood volume and pulmonary artery hypertension due to exertion. Evidence for a hemodynamic etiology also includes the observation that when swimming in the lateral decubitus position unilateral edema tends to occur in the dependent lung (39, 41).

IPE tends to occur in cold water (31), which is consistent with an augmented preload in the cold (34). It has been reported that individuals who have experienced IPE have an exaggerated vasoconstrictive response to cold (67), suggesting that during cold water immersion hydrostatic pulmonary edema results from the combination of increased afterload and preload. The most prevalent mechanism involves stress failure of pulmonary capillaries as a result of increased pulmonary vascular pressures (31, 38). Pulmonary artery pressure and pulmonary arterial wedge pressure (PAWP) both increase during immersion, and to a greater degree in cold water (66).

It has been shown that during underwater exercise at a fixed rate with a -15 cmH₂O static transrespiratory pressure load [P_{Tr} , “static lung load” (64)] ventilation does not stay constant, but rather increases beyond 12.5-min duration at 1.12 and 2.7 atm absolute (ATA) (53, 69). The investigators proposed that the increase in ventilation in untrained subjects may be caused by lactate accumulation in locomotor and/or respiratory muscles (54, 69) and possibly by systemic metabolic acidosis (53). Compared with exercise in the dry, underwater exercise is more likely to induce respiratory muscle fatigue because of increased resistive and elastic load (12, 52). Experimental evidence suggests that during heavy exercise the respiratory muscles may compete with the locomotor muscles for blood flow. During respiratory muscle fatigue blood flow to the locomotor muscles may be decreased (14, 56). Moreover, if the increased ventilation reflected a less efficient ventilatory pattern, metabolic acidosis could be compounded by respiratory acidosis. Metabolic and/or respiratory acidosis would be expected to increase pulmonary vascular resistance (PVR) and pressures (26, 63), and indeed this time frame (10–12 min) is consistent with the onset of IPE symptoms in many reported cases. Additionally, although during normocapnia hyperbaric hyperoxia has a vasodilatory effect on pulmonary vasculature at rest (44), this could be offset or eliminated by hypercapnia induced by hyperoxic depression of respiratory drive. Indeed, exercise under dry hyperbaric hyperoxic conditions [2.0 ATA inspired P_{O_2} ($P_{I_{O_2}}$)] is accompanied by increased arterial and venous P_{CO_2} compared with normoxia (35). Although a recent study observed no influence of P_{O_2} on ventilation in the range 0.7 ATA to 1.3 ATA $P_{I_{O_2}}$ during immersed exercise at 4.7

Address for reprint requests and other correspondence: R. E. Moon, Dept. of Anesthesiology, Box 3094, Duke Univ. Medical Center, Durham, NC 27710 (e-mail: richard.moon@duke.edu).

ATA (8), there have been no studies comparing normoxia ($P_{iO_2} = 0.2$) with the highest P_{iO_2} used in actual diving operations, 1.75 ATA.

In the present study, we tested the hypotheses that 1) the cause of the increase in ventilation during immersed exercise beyond 10-min duration is metabolic and respiratory acidosis, which induces a concomitant rise in pulmonary artery pressure, and 2) hyperoxia attenuates the increase in pulmonary artery pressure despite high P_{CO_2} during exercise at 4.7 ATA.

MATERIALS AND METHODS

Subject selection. After institutional approval and informed consent, 10 volunteer subjects were studied. Screening before the experimental days included medical history, physical examination, 12-lead electrocardiogram, posterior-anterior and lateral chest radiographs, measurement of vital capacity, forced expiratory volume (FEV) in 1 s (FEV₁), FEV at 25–75% of vital capacity (FEV_{25–75}), body fat by caliper skinfold measurement, aerobic capacity [maximal O₂ consumption ($\dot{V}O_{2max}$)] measured under dry conditions on a bicycle ergometer, and hypercapnic ventilatory response (HCVR) (8). $\dot{V}O_{2max} < 30 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, ratio of FEV₁ to forced vital capacity < 0.75 , or estimated body fat $> 3\%$ higher than the age- and sex-based upper limits (male $< 35 \text{ yr} = 25\%$, $\geq 35 \text{ yr} = 28\%$; female $< 35 \text{ yr} = 38\%$, $\geq 35 \text{ yr} = 41\%$), contraindications to diving (ear or sinus infection and inability to autoinflate the middle ear), and pregnancy were grounds for exclusion from the study. The aerobic fitness minimum threshold was established in order that the subject pool might reasonably model US Navy divers.

Chamber and conditions. Briefly, the experiment was conducted in a small water-filled pool (volume 4.42 m³) inside a hyperbaric chamber. Subjects exercised in the prone position, using an electronically braked ergometer as previously described (8). Inspired and expired gas was conducted to and from the subject via tubing connected to an adjacent chamber that was kept at a slightly higher pressure to compensate for the water depth and maintain P_{tr} at $\pm 3\text{--}4 \text{ cmH}_2\text{O}$.

Subjects were prone for immersed rest and exercise. Air temperature inside the chamber was maintained at 22–25°C. All trials were conducted in thermoneutral water (28.4–30.8°C) (11). Surface trials were conducted with the chamber at atmospheric pressure, typically 750 mmHg. Trials at depth were at 4.7 ATA (equivalent to a depth of 122 ft/37 m of seawater). The actual bottom time (time from leaving the surface to the start of decompression) during each experiment ranged from 41 to 68 min (median 48 min). Decompression tables were designed for the study by using 100% O₂ breathing with intermittent breaks during which the subjects breathed air.

Equipment. A mixing box made in-house was used to ensure homogeneous mixing of expired gas samples. A cylindrical mixing box was constructed of acrylic with nylon end-caps, dimensions of 63.5-cm length by 29.2-cm internal diameter, and volume of 45 liters with 7 baffles. After a step change in gas concentration at the intake, time to reach 90% of plateau value at the output at a flow of 60 l/min was calculated at 45 s assuming an exponential rise. The actual measured times were 37.4 s at surface and 40.6 s at 4.7 ATA. The mixing box was placed between the subject's breathing mask and the expiratory bag (200-l Douglas bag). Additional details of the apparatus were as previously described (8).

Instrumentation. At the start of each experiment, a radial artery catheter (20 gauge, Arrow International, Reading, PA) and a pulmonary artery (PA) catheter (model 131HF7 standard 4-lumen monitoring catheter with antimicrobial heparin coating, Edwards Lifesciences, Irvine, CA) were inserted. The PA catheter was inserted via an antecubital vein. Radiographic imaging was used to confirm that the tip was in a pulmonary artery (8).

Procedure. Each subject was submersed in water to ~50-cm depth measured at the midchest in the prone position and studied under the following conditions: 1) at rest at the surface, 2) during exercise at the surface, and 3) during exercise at a simulated depth of 37 m of seawater (4.7 ATA). The protocol, identical except for the gas mixture at depth, was repeated on a second study day. Experimental sessions for each subject were separated by 7–42 days (median 14 days). For the remainder of the text, “surface” is defined as 1 ATA and “depth” as 4.7 ATA.

All subjects breathed air for trials at the surface (21% O₂, or 0.21 ATA P_{O_2}). At depth, each subject breathed an O₂-N₂ gas mixture with 0.21 ATA P_{O_2} (4.3% O₂) and 1.75 ATA P_{O_2} (37% O₂), delivered during different experimental sessions in random order. Randomization of surface versus depth measurements could not be performed because of the risk of decompression illness (DCI) with heavy exercise immediately after diving.

After equilibration of gas in the mixing box with the subject's mixed expired gas, each trial at surface consisted of 6 min of resting measurements followed by 16 min of exercise measurements. Resting data were not collected at depth because of time constraints. For each resting trial, expired gas was collected during the 3rd to 6th minutes. Arterial and mixed venous (from the PA catheter) blood samples were collected anaerobically over a 15- to 20-s period during the sixth minute of rest.

Exercise levels were set at 100 W (externally measured power) for underwater exercise, and subjects pedaled at a rate of 60 rpm. Earlier studies had estimated the power required to move the legs through the water at ~50 W. For two subjects, external work rate was decreased to 75 W because of fatigue during the practice exercise sessions. For one subject, external work rate was increased to 175 W because of his very high exercise capacity. Expired gas was collected during the 5th, 6th, 15th, and 16th minutes of each exercise period. Arterial and mixed venous blood samples were collected anaerobically in heparinized glass syringes over a 15- to 20-s period during the 6th and 16th minutes.

Measurements. Monitoring and data collection were as previously described (8). ECG, arterial pressure, pulmonary arterial pressure, and central venous pressure were continuously recorded, with intermittent PAWP measurement. Mean arterial pressure (MAP), mean pulmonary arterial pressure (MPAP), and mean central venous pressure (CVP) were obtained by digital averaging.

Pressure transducers (Hospira, Lake Forest, IL) were positioned and maintained at the water surface level. The pressure of the chamber containing the breathing gases was maintained equal to the hydrostatic pressure at the subject's midchest level. Core body temperature was monitored by the PA catheter and recorded during the experiment. At the end of each experiment the digital output from the PA catheter was calibrated in water against an analytic thermometer.

Samples of arterial and mixed venous blood (3–4 ml) were drawn anaerobically and kept on ice until analysis ($\leq 30 \text{ min}$) (8). Each blood sample obtained at depth was maintained in ice within a polyvinyl chloride (PVC) pressurized container, removed via air lock, and analyzed by blood gas analyzer (Synthesis 15, Instrumentation Laboratory, Lexington, MA) and CO-oximeter (model 682, Instrumentation Laboratory) in a separate chamber pressurized to 18.2 m of seawater (2.82 ATA) as previously described (8). Total CO₂ was calculated according to a previously described method (7).

Mixed expired O₂ and CO₂ concentrations and fraction of end-tidal CO₂ (F_{etCO₂}) were measured with mass spectrometry (MS) (model 1100 medical gas analyzer, Perkin-Elmer, Pomona, CA) and confirmed by gas chromatography (GC) (model 3800, Varian, Palo Alto, CA) (8). During collection of expired gases, 500–1,000 ml of mixed expired gas was drawn from the mixing box into a glass syringe during the 5th, 6th, 15th, and 16th minutes for analysis by GC. For measurement of mixed expired gases at depth with 1.75 ATA P_{iO_2} , calibration gases (Airgas, Radnor, PA) over a narrow range of O₂ concentrations (33.8565%, 34.8511%, 35.9501%, 37.3167%) were

used. Mixed expired O_2 concentration was obtained by both MS and GC by bracketing the unknown gas with the two closest calibration gases.

Calibrations. Before each experimental run, the gasometer, blood gas analyzer, and CO-oximeter were calibrated. Because of the potential error in measurement of $\dot{V}O_2$ at high inspired O_2 fraction ($F_{I_{O_2}}$), the mass spectrometer was calibrated immediately before each run with the gases described above. The pressure transducers were calibrated with an aneroid gauge that had been precalibrated against a mercury manometer.

Calculations. Tidal volume (V_T) was calculated with measurements of minute ventilation (\dot{V}_E) and ventilatory frequency (f) and was converted to BTPS. Pulmonary artery temperature (T_{body}) at the surface was measured from the PA catheter thermistor and was used for BTPS corrections. At depth, the increase in ambient pressure caused the PA catheter thermistor to malfunction; thus during depth runs T_{body} was assumed to be $37.0^\circ C$. O_2 consumption ($\dot{V}O_2$) and CO_2 elimination ($\dot{V}CO_2$) rates were determined from standard equations using GC measurements. Fick cardiac output (CO) was calculated as $\dot{V}O_2/(Ca_{O_2} - Cv_{O_2})$, where Ca_{O_2} and Cv_{O_2} are the arterial and mixed venous O_2 contents, respectively. PVR was calculated as $80 \times (MPAP - PAWP)/CO$. PO_2 , PCO_2 , pH, and alveolar-arterial PO_2 ($PA_{O_2} - Pa_{O_2}$) difference were adjusted for T_{body} at the surface according to the National Committee for Clinical Laboratory Standards (3). For depth runs, blood gas values were reported as uncorrected for T_{body} . This was felt to be reasonable, as temperature increases during surface exercise were small and were expected to be attenuated at depth because of the higher thermal capacity of breathing gas at depth, which would tend to remove heat from alveolar capillary blood. Arterial and mixed venous base excess (BE) were calculated from hemoglobin, bicarbonate, and pH (59). Arterial and mixed venous hemoglobin and hematocrit values were corrected for the added heparin volume (0.3 ml).

Statistics. Effects of depth, PI_{O_2} , and exercise time on \dot{V}_E , f , V_T , alveolar ventilation (\dot{V}_A), fractional dead space (V_D/V_T), MPAP, PAWP, CO, CVP, PVR, MAP, heart rate (HR), arterial and mixed venous pH, bicarbonate, BE, PCO_2 , PO_2 , and $PA_{O_2} - Pa_{O_2}$ difference were analyzed by repeated-measures analysis of variance (mixed model, SAS Enterprise Guide 4.0, Cary, NC). Condition (surface, normoxia at depth, hyperoxia at depth) and time (early, late in exercise) were treated as categorical variables. Condition, time, and the interaction of condition with time were included as main effects, with subject as the within-subjects effect. Tukey adjustment was used for post hoc analysis of condition and time for all pairwise comparisons of significant predictors. The significance level was set at $\alpha = 0.05$. Results are displayed as means \pm SD.

RESULTS

Subjects. Subject characteristics appear in Table 1. No subjects were smokers. Of the 10 subjects studied, 9 completed all

exercise runs. One subject stopped before completion of the exercise session at depth with 0.21 ATA PI_{O_2} because of a sensation of air hunger, which resolved immediately after cessation of the exercise. There were no incidents of barotrauma or DCI. Two subjects developed phlebotrombosis in the arm of the catheter insertion—one was asymptomatic, and one became asymptomatic after a few days. No signs or symptoms of pulmonary edema were present in any subject.

Respiratory parameters. Under surface conditions, \dot{V}_E , f , V_T , and \dot{V}_A increased, and V_D/V_T decreased from rest to exercise ($P < 0.0001$ for all parameters). T_{body} (mean \pm SD) at rest was $36.7 \pm 0.6^\circ C$, in early exercise $37.3 \pm 0.5^\circ C$, and in late exercise $37.6 \pm 0.5^\circ C$.

\dot{V}_E , \dot{V}_A , f , V_T , and V_D/V_T during exercise trials are shown in Fig. 1. At the surface, \dot{V}_E increased from early to late exercise (12% increase, $P = 0.0004$). At depth, \dot{V}_E was decreased during normoxia (6.5% decrease from surface, $P = 0.01$) and further decreased by hyperoxia (16.3% decrease from normoxia at depth, $P < 0.0001$); however, there was no statistically significant change from early to late exercise (normoxia: 5.6% increase, $P = 0.07$; hyperoxia: 7.6% increase, $P = 0.08$).

V_T did not significantly change from early to late exercise ($P = 0.07$) and did not differ between conditions ($P = 0.47$). Changes in ventilation were reflected in f , which increased from early to late exercise at the surface (19.6% increase, $P = 0.0004$), decreased at depth (7.6% decrease from surface, $P = 0.02$), and further decreased with hyperoxia (16.9% decrease from normoxia at the surface, $P < 0.0001$; 10.0% decrease from normoxia at depth, $P = 0.006$).

V_D/V_T was increased by hyperoxia (15.5% increase from normoxia, $P = 0.002$) and was not affected by depth alone or by time during exercise. \dot{V}_A (calculated from V_D/V_T and \dot{V}_E) reflected changes in \dot{V}_E and was decreased by depth (11.5% decrease from surface, $P = 0.01$) and hyperoxia (21.7% decrease from normoxia at depth, $P < 0.0001$). \dot{V}_A increased from early to late exercise only at the surface (11.1% increase, $P = 0.005$).

HCVR in one subject. During prescreening, subject 3 was noted to have a remarkably low HCVR ($0.10 \text{ l}\cdot\text{min}^{-1}\cdot\text{mmHg}^{-1}$). Because low HCVR has been correlated with increased levels of arterial PCO_2 (Pa_{CO_2}) in divers (8), and extremely low HCVR has been reported to predict dangerous hypercapnia (48), we have chosen to include selected respiratory, hemodynamic, and blood gas parameters for this subject (see Table 4).

Cardiovascular parameters. Arterial, pulmonary artery, pulmonary artery wedge pressures and central venous waveforms

Table 1. Subject characteristics

Subject	Sex	Age, yr	Height, cm	Weight, kg	Estimated Body Fat, %	$\dot{V}O_{2max}$, $\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$	HCVR, ($\text{l}\cdot\text{min}^{-1}\cdot\text{mmHg}^{-1}$)	FVC, liters
1	M	23	182.9	67.05	9.90	57.4	1.93	6.14
2	M	34	182.9	90.75	16.00	40.0	1.25	6.00
3	M	27	177.8	63.05	9.20	44.2	0.10	5.29
4	M	44	177.8	87.50	18.90	36.8	0.90	6.20
5	M	26	188.0	86.85	13.70	44.4	2.11	5.73
6	M	27	176.5	75.60	6.90	62.0	2.65	5.40
7	F	25	175.3	68.20	23.90	34.7	0.97	3.92
8	M	20	170.8	70.30	7.10	44.3	1.05	4.18
9	F	29	166.4	65.05	23.80	40.3	0.76	4.44
10	M	33	170.2	80.10	18.60	37.6	1.66	5.89
Mean \pm SD		28.8 \pm 6.8	176.9 \pm 6.6	75.5 \pm 10.2	14.8 \pm 6.5	44.2 \pm 8.9	1.3 \pm 0.8	5.3 \pm 0.9

$\dot{V}O_{2max}$, maximal O_2 uptake; HCVR, hypercapnic ventilatory response; FVC, forced vital capacity; M, male; F, female.

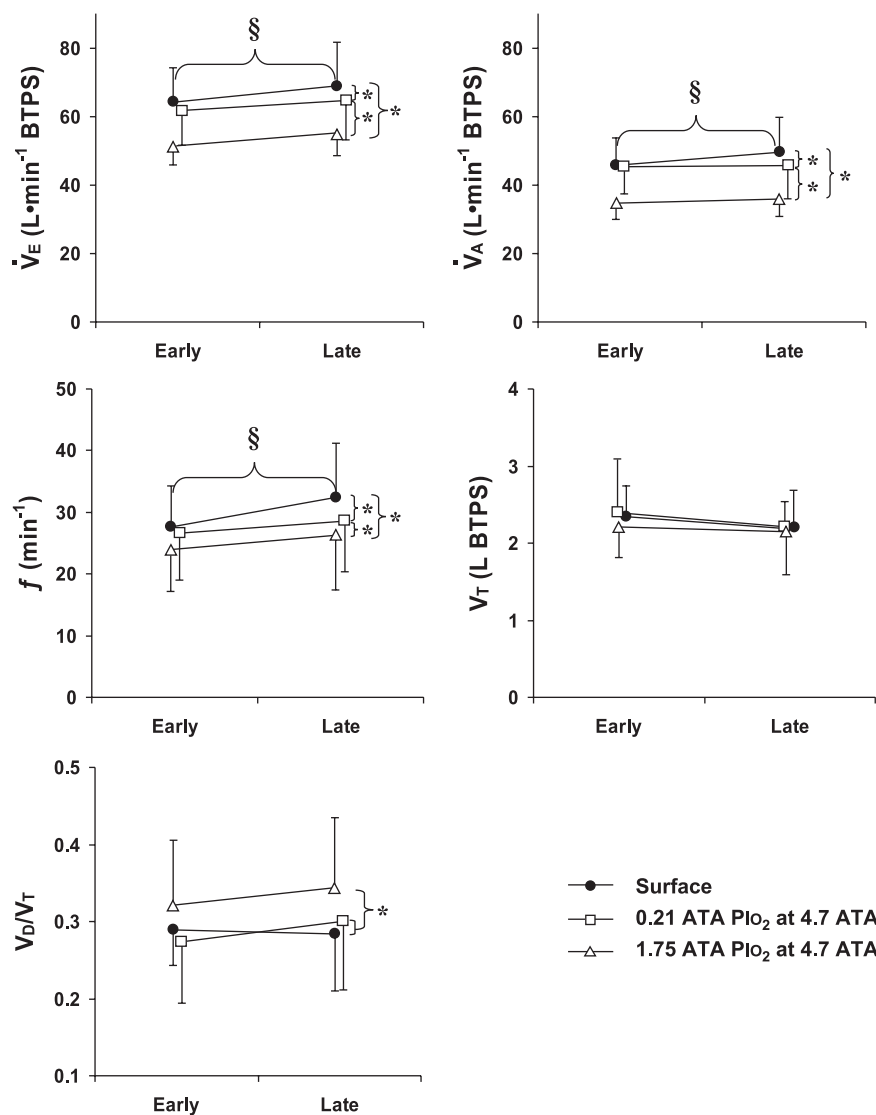


Fig. 1. Minute ventilation (\dot{V}_E), alveolar ventilation (\dot{V}_A), ventilatory frequency (f), tidal volume (V_T), and fractional dead space (V_D/V_T) during exercise trials. Early, 6 min of exercise; late, 16 min of exercise. \dot{V}_E increased from early to late exercise at the surface, but not at depth. \dot{V}_E was reduced by depth and further reduced by hyperoxia. V_T did not significantly change from early to late exercise and did not differ between conditions; f increased from early to late exercise at the surface and was reduced by depth and further reduced by hyperoxia. V_D/V_T was increased by hyperoxia and was not affected by depth alone or by continued exercise. \dot{V}_A increased from early to late exercise only at the surface. \dot{V}_A was reduced by depth and hyperoxia. Mean values \pm SD are shown. *Statistical significance ($P < 0.05$) between a pair of conditions; §significant difference ($P < 0.05$) between early and late exercise at the surface. PiO_2 , inspired PO_2 ; ATA, atmospheres absolute.

were obtained from all subjects. Exercise, compared with rest, significantly increased HR, MAP, CO, and MPAP ($P < 0.0001$). PVR and systemic vascular resistance (SVR) significantly decreased from rest ($P = 0.04$ and < 0.001 , respectively). Stroke volume (SV; $P = 0.15$), CVP ($P = 1.0$), and

PAWP ($P = 0.26$) did not differ significantly from rest to exercise.

Effects of depth on systemic hemodynamics. Systemic hemodynamic results are shown in Table 2. In normoxia, compared with the surface, at depth there were increases in HR

Table 2. Systemic hemodynamic results during rest and exercise

	Surface			Normoxia at Depth		Hyperoxia at Depth	
	Rest	Early	Late	Early	Late	Early	Late
HR, beats/min	62 \pm 13	131 \pm 15*	147 \pm 15*†	139 \pm 16‡	152 \pm 14†‡	127 \pm 16‡§	137 \pm 18†‡§
MAP, mmHg	98.5 \pm 7.2	117.5 \pm 7.2*	110.8 \pm 6.0*†	119.2 \pm 8.4‡	115.4 \pm 8.4†‡	115.0 \pm 6.6§	112.8 \pm 6.4†§
CVP, mmHg	5.9 \pm 1.6	5.9 \pm 3.3	3.9 \pm 3.0	8.3 \pm 6.2‡	8.1 \pm 6.0‡	7.3 \pm 3.6§	5.4 \pm 4.1§
SVR, dyn·s·cm ⁻⁵	1,569.6 \pm 585.1	623.5 \pm 111.0*	568.6 \pm 91.3*	501.9 \pm 181.5‡	460.1 \pm 110.9‡	511.8 \pm 79.0‡	517.5 \pm 111.2‡
SV, ml	91.8 \pm 38.1	113.1 \pm 25.4	104.6 \pm 24.5	154.8 \pm 73.6‡	122.4 \pm 17.7‡	137.7 \pm 27.6‡	124.9 \pm 23.7‡
$\dot{V}O_2$, l/min STPD	0.35 \pm 0.12	2.14 \pm 0.34*	2.26 \pm 0.43*	2.22 \pm 0.58	2.30 \pm 0.52	2.14 \pm 0.51	2.14 \pm 0.34
$\dot{V}CO_2$, l/min STPD	0.29 \pm 0.09	2.11 \pm 0.31*	2.14 \pm 0.35*	2.14 \pm 0.38	2.08 \pm 0.26	1.86 \pm 0.28‡§	1.96 \pm 0.32‡§

Values are means \pm SD. Surface, air, 1.0 atm absolute (ATA); normoxia at depth, 0.2 ATA, inspired PO_2 (PiO_2), 4.7 ATA; hyperoxia at depth, 1.75 ATA PiO_2 , 4.7 ATA; Rest, resting values; Early, exercise values, 6 min; Late, exercise values, 16 min; HR, heart rate; MAP, mean arterial pressure; CVP, central venous pressure; SV, stroke volume; SVR systemic vascular resistance; $\dot{V}O_2$, O_2 consumption rate; $\dot{V}CO_2$, CO_2 elimination rate. Significant difference ($P < 0.05$): *from rest to exercise; †from early to late exercise; ‡depth compared with surface; §hyperoxia compared with normoxia at depth.

(4.2% increase, $P = 0.009$), MAP (3.0% increase, $P = 0.007$), CVP (66.0% increase, $P = 0.002$), CO (20.2% increase, $P = 0.009$, Fig. 2), and SV (28.3% increase from surface, $P = 0.007$). On the other hand, SVR was decreased at depth (19.3% decrease from surface, $P = 0.01$).

Effects of hyperoxia on systemic hemodynamics. Hyperoxia decreased HR compared with normoxia at depth (9.0% decrease, $P < 0.0001$) and compared with surface (5.2% decrease, $P = 0.0007$). The increase in MAP from surface to depth was abolished by hyperoxia at depth ($P = 0.82$, depth hyperoxia compared with surface). The increase in CVP at depth was abolished by hyperoxia. At depth, hyperoxia did not induce any significant change in CO ($P = 0.39$), SVR ($P = 0.65$) or SV ($P = 0.42$).

Effects of sustained exercise on systemic hemodynamics. HR increased significantly from early to late exercise (9.6% increase, $P < 0.0001$). There was a statistically significant decrease in MAP from early to late exercise (3.5% decrease, $P = 0.02$). There was no significant change from early to late exercise in CO ($P = 0.59$), CVP ($P = 0.08$), SVR ($P = 0.33$), or SV ($P = 0.07$) across all P_{O_2} and depth conditions.

Effects of depth, hyperoxia, and sustained exercise on pulmonary hemodynamics. MPAP, PAWP, CO, and PVR during exercise trials are shown in Fig. 2. In normoxia, MPAP was increased by depth (19% increase, $P = 0.001$). This increase was not seen in with hyperoxia at depth. Measurement of MPAP at 1-min intervals during exercise showed a decrease in MPAP from early to late exercise that was significant at the surface ($P = 0.003$) but not at depth. Interindividual variation in MPAP was wide (range 16.0–39.6 mmHg at the surface, 14.1–42.1 mmHg in normoxia at depth, and 16.6–36.0 mmHg

in hyperoxia at depth) (see Fig. 3). PAWP did not differ among conditions or from early to late exercise.

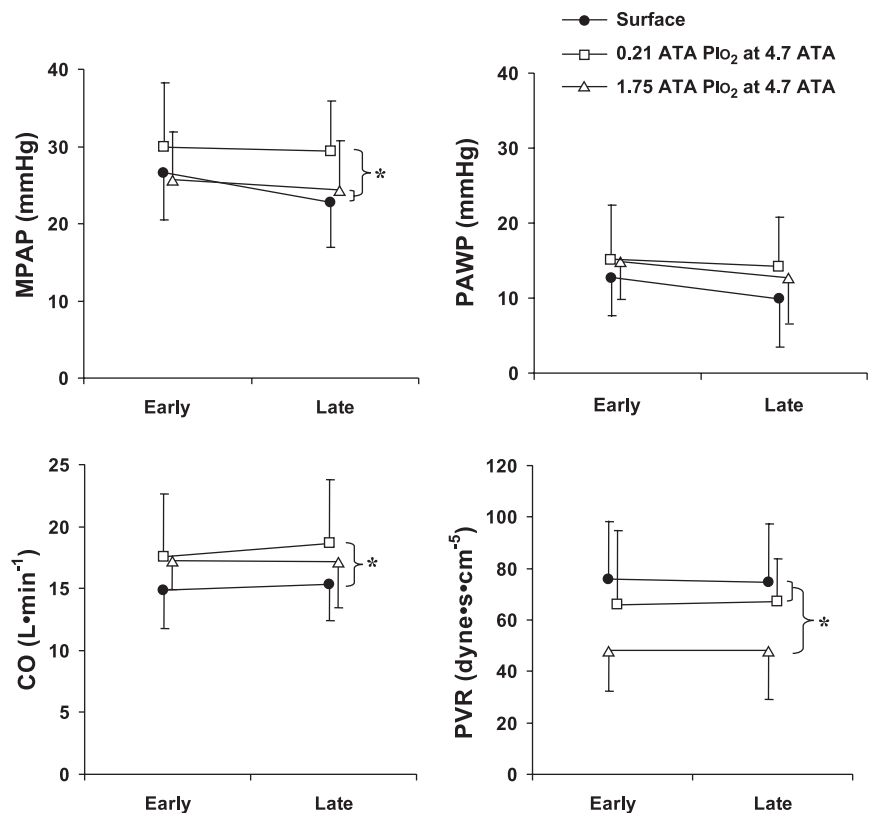
In normoxia, PVR was not significantly affected by depth ($P = 0.21$). At depth, hyperoxia decreased PVR compared with normoxia (27.9% decrease, $P < 0.009$). There was no change in PVR from early to late exercise ($P = 0.99$).

$\dot{V}O_2$ and $\dot{V}CO_2$ results are shown in Table 2. $\dot{V}O_2$ during exercise was $\sim 65\%$ of mean $\dot{V}O_{2max}$ for subjects and was not affected by depth ($P = 0.51$) or P_{O_2} ($P = 0.28$). There was no difference in $\dot{V}O_2$ from early to late exercise ($P = 0.44$). In normoxia, $\dot{V}CO_2$ was not affected by depth ($P = 0.58$). Hyperoxia decreased $\dot{V}CO_2$ compared with normoxia (at depth, 11.0% decrease from normoxia, $P < 0.0001$ 9.9% decrease compared with surface, $P = 0.0001$). There was no change in $\dot{V}CO_2$ from early to late exercise ($P = 0.21$).

Blood gas parameters. At surface, from rest to exercise, arterial pH, bicarbonate, total CO_2 (TCO_2), and BE decreased significantly ($P = 0.0003$ for pH, $P < 0.0001$ for bicarbonate and BE, $P = 0.004$ for TCO_2). $PaCO_2$ and PaO_2 did not change significantly from rest to exercise ($P = 0.20$ and $P = 0.58$, respectively) (Table 3). Mixed venous pH and BE decreased significantly from rest to exercise ($P < 0.0001$ and $P = 0.01$, respectively), but mixed venous bicarbonate and TCO_2 did not ($P = 0.89$ for bicarbonate, $P = 0.91$ for TCO_2).

PaO_2 , $PaCO_2$, arterial pH, bicarbonate, BE, and TCO_2 during exercise trials are shown in Table 3. Arterial pH, BE, TCO_2 , and bicarbonate did not change from early to late exercise. Arterial pH did not differ among depth or P_{O_2} conditions ($P = 0.31$). Arterial BE during exercise was increased (less negative) in normoxia at depth compared with the surface ($P = 0.0007$) and further increased in hyperoxia at depth ($P <$

Fig. 2. Mean pulmonary artery pressure (MPAP), pulmonary arterial wedge pressure (PAWP), cardiac output (CO), and pulmonary vascular resistance (PVR) during exercise trials. Early, 6 min of exercise; late, 16 min of exercise. During normoxia, MPAP was increased by depth. This increase was attenuated by hyperoxia. PAWP did not differ among conditions or from early to late exercise. In normoxia, CO was increased by depth, an effect that was attenuated by hyperoxia. There was no significant change in CO from early to late exercise. PVR was decreased by hyperoxia but not by depth alone. There was no change in PVR from early to late exercise. Mean values \pm SD are shown. *Statistical significance ($P < 0.05$) between a pair of conditions.



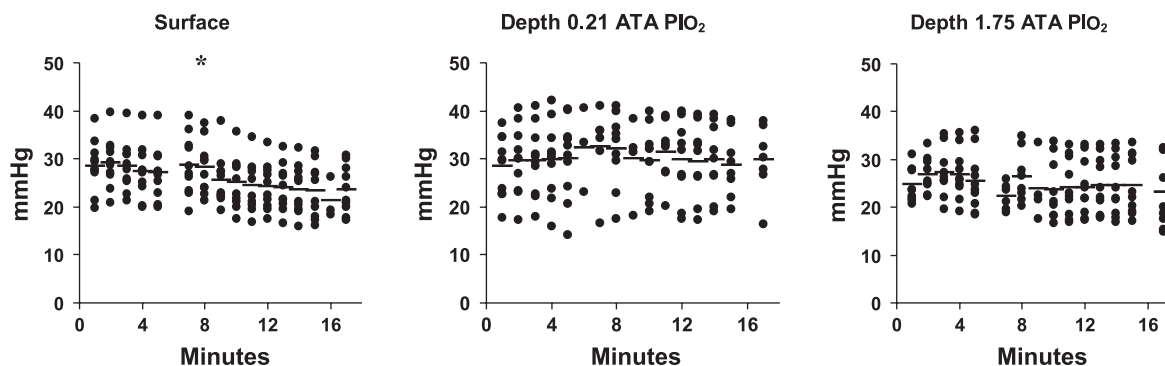


Fig. 3. MPAP during exercise trials. Each circle represents a single measurement for a subject. The mean for all subjects at each time point is indicated by a horizontal bar. Measurement of MPAP at 1-min intervals during exercise showed a decrease in MPAP from early to late exercise that was significant at the surface ($P = 0.003$) but not at depth. Interindividual variation in MPAP was wide (range 16.0–39.6 mmHg at the surface, 14.1–42.1 mmHg in normoxia at depth, and 16.6–36.0 mmHg in hyperoxia at depth).

0.0001). Arterial bicarbonate was increased by depth (12.2% increase from surface, $P < 0.0001$) and further increased by hyperoxia at depth (12.8% from normoxia at depth, $P < 0.0001$). Arterial TCO_2 was increased by depth (12.5% increase from surface, $P = 0.0002$) and further increased by hyperoxia at depth (12.6% increase from normoxia at depth, $P < 0.0001$).

PAO_2 - PaO_2 difference during exercise trials is shown in Fig. 4. In normoxia, there was no effect of depth on the PAO_2 - PaO_2 difference ($P = 0.09$). From early to late exercise, the PAO_2 - PaO_2 difference increased 51.5% in normoxia ($P = 0.02$) but did not change significantly during hyperoxia.

In normoxia, mean PaO_2 was constant at $\sim 101.6 \pm 10.1$ mmHg with no significant change at depth ($P = 0.16$) or from early to late exercise ($P = 0.06$). In hyperoxia, mean PaO_2 was $1,061.7 \pm 56.4$ mmHg, with no significant change from early to late exercise ($P = 0.67$). PaCO_2 increased significantly with depth (12.8% increase, $P < 0.0001$) and further with hyperoxia at depth (10.8% increase from normoxia at depth, $P < 0.0001$). There was no statistically significant change in PaCO_2 from early to late exercise ($P = 0.06$). The interaction term between depth and PO_2 conditions with exercise was not significant ($P = 0.10$).

Mixed venous pH did not differ among depth or PO_2 conditions ($P = 0.90$) or from early to late exercise ($P = 0.65$). mixed venous PO_2 ($\text{P}\bar{\text{v}}\text{O}_2$) was increased by depth (30.5% increase from surface, $P < 0.0001$) and further increased by hyperoxia (5.4% increase from normoxia at depth, $P = 0.03$). There was no difference from early to late exercise in $\text{P}\bar{\text{v}}\text{O}_2$ ($P = 0.30$) or mixed venous PCO_2 ($\text{P}\bar{\text{v}}\text{CO}_2$) ($P = 0.14$). $\text{P}\bar{\text{v}}\text{CO}_2$ was increased by depth (5.5% increase from surface, $P = 0.03$), with no further effect of hyperoxia compared with normoxia at depth ($P = 0.95$). Mixed venous TCO_2 was increased by depth (6.1% increase from surface, $P = 0.008$) and further increased by hyperoxia at depth (7.6% increase from normoxia at depth, $P = 0.0007$).

DISCUSSION

In this investigation of sustained immersed exercise over the PiO_2 range of 0.2 to 1.75 ATA, we found that the increase in ventilation seen at the surface was not related to changes in blood gases (i.e., acidosis). Pulmonary vascular pressures showed very wide individual variability (range = 14.1–42.1 mmHg) and were increased at depth in normoxia compared with surface, an effect that was attenuated by hyperoxia.

Table 3. Blood gas results during rest and exercise

	Surface			Normoxia at Depth		Hyperoxia at Depth	
	Rest	Early	Late	Early	Late	Early	Late
Arterial blood gases							
PaO_2 , mmHg	103.9 ± 7.6	105.2 ± 6.4	102.1 ± 8.4	103.8 ± 13.6	94.7 ± 8.7	$1,056 \pm 51\ddagger\text{\$}$	$1,067 \pm 64\ddagger\text{\$}$
PaCO_2 , mmHg	40.1 ± 3.8	39.3 ± 2.3	36.1 ± 3.5	$42.8 \pm 3.0\ddagger$	$42.0 \pm 3.7\ddagger$	$47.2 \pm 3.2\ddagger\text{\$}$	$47.0 \pm 3.8\ddagger\text{\$}$
pH	7.41 ± 0.02	$7.32 \pm 0.05^*$	$7.32 \pm 0.06^*$	7.32 ± 0.05	7.31 ± 0.08	7.32 ± 0.04	7.33 ± 0.06
Bicarbonate, mmol/l	25.4 ± 2.1	$20.5 \pm 2.9^*$	$18.9 \pm 4.0^*$	$22.4 \pm 3.3\ddagger$	$21.5 \pm 4.2\ddagger$	$24.9 \pm 2.8\ddagger\text{\$}$	$25.0 \pm 2.7\ddagger\text{\$}$
Base excess, mmol/l	0.6 ± 1.7	$-5.0 \pm 3.4^*$	$-6.3 \pm 4.5^*$	$-3.1 \pm 3.7\ddagger$	$-4.2 \pm 5.0\ddagger$	$-1.0 \pm 3.0\ddagger\text{\$}$	$-0.9 \pm 3.2\ddagger\text{\$}$
Total CO_2 , mmol/l	27.7 ± 2.2	$21.7 \pm 2.9^*$	$19.9 \pm 4.0^*$	$23.7 \pm 3.3\ddagger$	$22.8 \pm 4.2\ddagger$	$26.4 \pm 2.9\ddagger\text{\$}$	$26.4 \pm 2.8\ddagger\text{\$}$
Mixed venous blood gases							
pH	7.36 ± 0.02	$7.22 \pm 0.06^*$	$7.23 \pm 0.06^*$	7.23 ± 0.06	7.23 ± 0.08	7.23 ± 0.04	7.23 ± 0.05
$\text{P}\bar{\text{v}}\text{O}_2$, mmHg	35.5 ± 4.8	$23.8 \pm 2.2^*$	$23.3 \pm 2.5^*$	$28.5 \pm 8.1\ddagger$	$26.1 \pm 2.5\ddagger$	$35.4 \pm 1.5\ddagger\text{\$}$	$35.4 \pm 2.5\ddagger\text{\$}$
$\text{P}\bar{\text{v}}\text{CO}_2$, mmHg	44.5 ± 4.1	$62.1 \pm 4.3^*$	$59.0 \pm 4.0^*$	$62.4 \pm 3.2\ddagger$	$60.9 \pm 5.0\ddagger$	$66.4 \pm 6.3\ddagger$	$67.6 \pm 6.2\ddagger$
Total CO_2 , mmol/l	26.7 ± 1.7	27.2 ± 2.6	26.4 ± 3.6	$28.8 \pm 3.2\ddagger$	$27.7 \pm 3.9\ddagger$	$30.3 \pm 3.5\ddagger\text{\$}$	$30.9 \pm 3.4\ddagger\text{\$}$

Values are means \pm SD. Surface, air, 1.0 ATA pH, PO_2 , and PCO_2 are corrected for body temperature; normoxia at depth, 0.2 ATA PiO_2 , 4.7 ATA; hyperoxia at depth, 1.75 ATA PiO_2 , 4.7 ATA; rest, resting values; early, exercise values, 6 min; late, exercise values, 16 min; PaO_2 , arterial PO_2 ; PaCO_2 , arterial PCO_2 ; pvo2mix , mixed venous PO_2 ; pvco2mix , mixed venous PCO_2 . Significant difference ($P < 0.05$): *from rest to exercise at the surface; \ddagger at depth compared with surface; $\text{\$}$ hyperoxia compared with normoxia at depth.

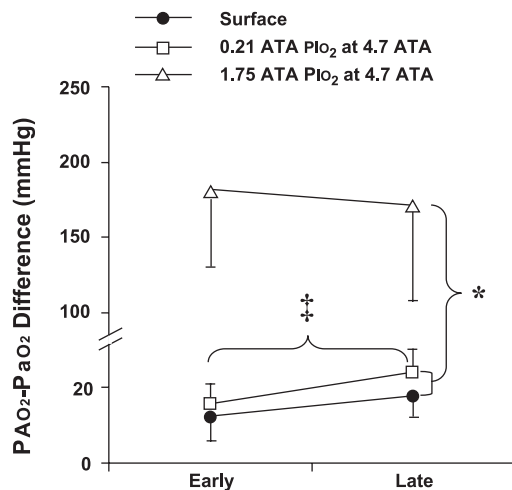


Fig. 4. Alveolar-arterial PO_2 ($P_{AO_2}-P_{aO_2}$) difference. In normoxia, there was no effect of depth on the $P_{AO_2}-P_{aO_2}$ difference. From early to late exercise, the $P_{AO_2}-P_{aO_2}$ difference increased 51.5% in normoxia but not in hyperoxia. Mean values \pm SD are shown. *Statistical significance ($P < 0.05$) between a pair of conditions; ‡statistically significant difference ($P < 0.05$) between early and late exercise.

Ventilation. At the surface, ventilation increased from early (6th min) to late (16th min) exercise, consistent with results of Wylegala et al. (69) for underwater exercise at 1.12 ATA. This increase occurred in the setting of constant workload, CO_2 , \dot{V}_{O_2} , and \dot{V}_{CO_2} . This increase in ventilation of $\sim 12\%$ occurred with \dot{V}_{O_2} in exercise of $\sim 65\%$ of subjects' demonstrated $\dot{V}_{O_{2max}}$. This amount of change in \dot{V}_E is comparable to that seen in sustained, constant-load exercise in the dry at a higher work rate of 85% of $\dot{V}_{O_{2max}}$ (28). Sustained, constant-load exercise in the dry at lower work rates ($\sim 45\text{--}65\%$ of $\dot{V}_{O_{2max}}$) produces a much more gradual increase or no change at all (30, 43). The difference in ventilatory pattern seen in immersed exercise compared with exercise in the dry is most likely due to increased resistive load caused by higher breathing gas density and increased elastic load caused by increase blood volume in the pulmonary vasculature (12, 52), factors that increase work of breathing (WOB).

Although \dot{V}_E tended to increase from early to late exercise at depth, the effect was not statistically significant. Similarly, Ray et al. showed that the increase in \dot{V}_E during underwater exercise at 2.7 ATA (53) and 4.7 ATA (54) was attenuated compared with studies at 1.12 ATA (69). It is likely that this attenuation of the increase in \dot{V}_E at 4.7 ATA in our study occurred by mechanisms similar to those in the studies by Ray et al. at depth. These include increased airway resistance due to higher gas density and hyperoxia [1.6 ATA P_{iO_2} was used in the studies by Ray et al. (53, 54)].

Ventilation and gas exchange. The increase in \dot{V}_E at the surface from early to late exercise was due to an increase in f without a significant change in V_T , although there was a trend toward a reduction in V_T in late exercise. From early to late exercise, there was no significant change in arterial or mixed venous pH or arterial bicarbonate to suggest increasing, uncompensated metabolic acidosis. P_{aCO_2} at the surface decreased concurrently with increasing \dot{V}_E as expected. V_D/V_T and \dot{V}_{O_2} did not change from early to late exercise, suggesting that these were not significant factors in driving ventilatory

changes during exercise in the present study. Exercise-induced respiratory muscle fatigue during dry exercise seems to occur as a result of increased WOB in the setting of limited perfusion of respiratory muscles (14) and has been suggested as a factor that contributes to the rise in \dot{V}_E during prolonged underwater exercise (53, 69). Increased respiratory rate is an early manifestation of inspiratory muscle fatigue in the clinical setting, a course in which the end point is often hypercapnic respiratory failure (10). In the present study, the increase in f is consistent with the onset of respiratory muscle fatigue due to increased resistive and elastic load; however, it did not result in changes in acid-base balance. We did not specifically investigate respiratory muscle fatigue. However, the increase in \dot{V}_E that we observed at the surface in the face of a constant metabolic load and blood gas parameters is consistent with respiratory muscle fatigue. More specific investigations have demonstrated a similar increase in \dot{V}_E associated with respiratory muscle fatigue in dry exercise (28). Respiratory muscle fatigue is also supported by the investigations of Wylegala et al. (69), who showed that the progressive increase in \dot{V}_E during steady-state exercise was eliminated by respiratory muscle training.

During constant-load exercise of light to moderate intensity in the dry at 1 ATA, \dot{V}_E increases sharply in the first minute of exercise and reaches a maximal value within 4 min and then remains constant, whereas at higher intensity \dot{V}_E continues to increase slowly after the initial sharp increase (30, 43, 49, 65). The increase in \dot{V}_E during submaximal immersed exercise at 1 ATA seen in the present study is more similar to changes in \dot{V}_E during moderate to heavy constant-load dry exercise. Response to acidosis (65), development of respiratory muscle fatigue (30), increased body temperature (23), and increased dead space (43) have been proposed as mechanisms for this increase seen in exercise at higher intensity in the dry. This difference in \dot{V}_E between dry and immersed exercise may reflect increased elastic WOB due to engorgement of pulmonary vessels during immersion (resulting in decreased lung compliance) (12, 52). It is also possible that the hyperventilation reflects activation of unmyelinated c fibers, which stimulate rapid, shallow breathing in response to increased lung water and pulmonary vascular congestion (J receptors) (22, 50), although if this were the main factor, it would be more difficult to explain the effects of respiratory muscle training (53, 54). It is likely that the same tendency for \dot{V}_E to increase during immersed exercise at the surface also exists at depth; however, mechanisms that potentiate hypoventilation, such as increased PO_2 and breathing gas density, may in part negate the effects seen at the surface.

In normoxia, V_D/V_T was similar at depth and at the surface, but in hyperoxia V_D/V_T was increased compared with the other conditions. Previous studies in the dry have shown V_D/V_T to increase with gas density, independent of PO_2 over the range of 0.2–3 ATA P_{iO_2} (8, 44, 47, 57, 58, 68), most likely because of impaired molecular diffusion of CO_2 and maldistribution of ventilation (47). This density-related increase in V_D/V_T was not seen in the present study of immersed exercise. Increased V_D/V_T seen in hyperoxia may be due to pulmonary vasodilatation, which could have resulted in diversion of blood flow to hypoventilated lung units (44).

Arterial P_{CO_2} was significantly increased by depth and further increased by hyperoxia at depth. A previous study of underwater exercise under the same conditions at 4.7 ATA

using P_{iO_2} 0.7, 1, and 1.3 ATA did not show any effect of P_{O_2} on P_{aCO_2} (8). However, the effect seen in the present study is likely to be due to the wider range of P_{O_2} . This is the first immersed exercise study to examine the effects of P_{iO_2} over this range.

Factors that could contribute to lower \dot{V}_E in hyperoxia at depth include a reduction in metabolic acidosis (due to less hypoxia-induced tissue acidosis) (35) or a direct inhibitory effect of hyperoxia on respiratory drive. Arterial pH during exercise was lower than normal and did not differ among surface, normoxia at depth, and hyperoxia at depth. However, the mechanisms of acidemia differed, with metabolic acidosis more prominent in normoxia. Depression of \dot{V}_E by hyperoxia resulted in a higher P_{aCO_2} compared with normoxia at depth and compared with surface. Studies of submaximal steady-state exercise O_2 breathing at 3 ATA compared with air breathing at 1 ATA revealed increased P_{aCO_2} in hyperoxia, which was attributed to a reduction in \dot{V}_{CO_2} (29). \dot{V}_{CO_2} in the present study was reduced by hyperoxia without a change in \dot{V}_{O_2} consistent with altered metabolic activity in respiratory muscles or reduced buffering of metabolic acids. Our blood gas findings indeed support a slight reduction in metabolic acids by hyperoxia, without an effect on arterial pH. Conceivably this could also be caused by an accumulation of CO_2 in the body due to reduced \dot{V}_A . Consistent with this, we did observe higher arterial TCO_2 and a trend toward increased mixed venous TCO_2 . Moreover, during hyperoxia elimination of CO_2 from tissue could have been impaired, because of reduced CO_2 solubility in venous blood attributable to the Haldane effect.

Direct suppression of respiratory drive by hyperoxia cannot be excluded as a cause for relative hypoventilation and hypercapnia (18, 35). The present study demonstrates a reduction of \dot{V}_E and \dot{V}_A in hyperoxia during underwater exercise at depth. That \dot{V}_E was reduced in hyperoxia despite an arterial pH similar to that in normoxic conditions and a higher P_{aCO_2} (which itself would be expected to stimulate \dot{V}_E via peripheral chemoreceptors) supports the notion of an attenuation of respiratory drive by hyperoxia. In addition, impairment of ventilation-perfusion (\dot{V}_A/Q) matching in hyperoxia, as suggested by diminished \dot{V}_A and greater \dot{V}_D/\dot{V}_T , may further contribute to CO_2 retention during exercise at depth.

HCVR in one subject. Subject 3 was noted to have a remarkably low HCVR at rest. Previous studies found HCVR to have a small, but significant effect on P_{aCO_2} , that is, low HCVR was associated with higher P_{aCO_2} (8, 36, 37). In the present study, this subject with impressively low HCVR did not demonstrate evidence of significant hypercapnia; in fact, his P_{aCO_2} values

were below the mean for all subjects (Table 4). This may have been due to his greater degree of metabolic acidosis (lower arterial pH and bicarbonate) compared with the mean, which could have offset his low CO_2 drive. Although this subject did not excessively retain P_{aCO_2} during moderate exercise in the study, the possibility that his P_{aCO_2} might have been higher during lighter exercise with less acidosis cannot be excluded.

Systemic hemodynamics. HR, CO, SV, MAP, and CVP were increased by depth compared with surface, effects that were abolished by hyperoxia. With P_{O_2} constant at 0.2 ATA at surface and depth, the main difference between these conditions is the increased density of breathing gas at depth, which will produce higher airway resistance and increased intrathoracic pressure swings between inspiration and expiration. Greater negative intrathoracic pressure during inspiration increases right ventricular preload, although this effect may be limited by the tendency for the great veins to collapse upon entry into the thorax (55), while positive intrathoracic pressure generated during expiration decreases left ventricular afterload (27, 51). These interactions would serve to augment SV. In humans during dry maximal exercise, reduction of intrathoracic pressure swings decreased CO and SV, while augmentation did not alter CO (21). During submaximal exercise in dogs augmentation of inspiratory negative pressure had little effect on CO, while reduction in the magnitude of inspiratory intrathoracic pressures swings (by applying positive pressure ventilation) reduced CO (46). During immersed submaximal exercise, engorgement of large veins (12, 52) would reduce the tendency for venous collapse at entry into the thorax during inspiration, thus allowing a greater degree of inspiratory preload augmentation. In addition, increased intra-abdominal pressure swings with increased WOB during exercise at depth would cause greater blood shift from the splanchnic vasculature to augment venous return and SV, and consequently the greater CO we saw at depth in this study (2). In the present study, increased HR and SV (compared with surface) both contributed to a higher CO at depth. Higher CVP compared with surface is consistent with increased preload, which would work to augment SV. A reduction of WOB by hyperoxia at depth would have attenuated such an increase in CO, which was indeed seen in this study.

From early to late exercise, HR increased despite constant workload and CO. A decrease in SV from early to late exercise approached statistical significance ($P = 0.07$). In upright exercise in the dry, SV reaches a plateau within the first 10 min during prolonged exercise (duration 50 min) at moderate-heavy submaximal workloads or tends to decrease because of shorter

Table 4. Respiratory and blood gas parameters for subject 3 during exercise (HCVR 0.10 l/mmHg)

	\dot{V}_E , l/min BTSP	P_{aCO_2} , mmHg	P_{aO_2} , mmHg	Arterial pH	Arterial Bicarbonate, mmol/l	\dot{V}_{O_2} , l/min STPD	\dot{V}_{CO_2} , l/min STPD
Surface							
Early	70.0	39.5	105	7.21	15.8	2.15	2.56
Late	78.8	30.7	112	7.20	11.9	2.17	2.19
Normoxia at depth							
Early	80.9	41.6	119	7.19	16.0	2.34	2.77
Late	89.0	37.7	104	7.13	12.7	2.48	2.51
Hyperoxia at depth							
Early	56.5	43.2	1006	7.23	18.5	2.78	2.23
Late	64.9	45.6	1082	7.21	18.2	2.89	2.33

Normoxia at depth, 0.2 ATA P_{iO_2} , 4.7 ATA; hyperoxia at depth, 1.75 ATA P_{iO_2} , 4.7 ATA; rest, resting values; early, exercise values, 6 min; late, exercise values, 16 min; \dot{V}_E , minute ventilation.

diastolic filling times with higher HR, and the maintenance of CO is HR dependent (13, 16, 24). CVP did not change from early to late exercise. MAP decreased from early to late exercise, consistent with observations during dry exercise at the surface, which is thought to occur because of vasodilatation for dissipation of heat and redistribution of blood to working muscles, although the decrease in SVR did not reach statistical significance (40).

Pulmonary hemodynamics during exercise. Previous work has shown that MPAP and PAWP increase during underwater exercise compared with dry exercise (66). In this study, however, comparing the 6th and 16th minutes of exercise, MPAP did not increase, and there was no change in PAWP, PVR, or CO from early to late exercise at surface or at depth. In addition, MPAP at the surface, analyzed at 1-min intervals, actually exhibited a significant decrease over the course of exercise but still exceeded what has been observed under similar conditions in the dry.

During dry exercise in healthy subjects, pulmonary artery pressure increases at the onset of exercise (within the first min) because of an increase in cardiac output, attains a peak pressure early in exercise (within 3–4 min), and stabilizes at a level at or below maximal pressure over the remainder of exercise (6–20 min total), as PVR decreases with recruitment of a greater proportion of pulmonary vessels (4, 5, 33, 60, 62). The decrease in PVR is not consistently observed: some investigators have found a decrease in MPAP and PAWP without change in PVR in steady-state submaximal exercise in the dry (62). To our knowledge, the present study is the first to report directly measured pulmonary artery pressures during prolonged underwater exercise. The finding of decreasing MPAP at the surface with prolonged underwater exercise is consistent with a progressive decrease in vascular tone, perhaps due to changing concentrations of a mediator of pulmonary vasodilatation. Endothelial nitric oxide (NO) is a known mediator of pulmonary vascular tone at rest and has been implicated in exercise-induced pulmonary vasodilatation in some animal species (in swine, not in horse or sheep) (15, 32, 42, 45). The release of NO induced by shear stress on pulmonary endothelial cells during exercise may play a role in the progressive decrease in MPAP at the surface seen in the present study. This effect could have been attenuated at depth by CO and blood gases (see below).

Pulmonary hemodynamics with depth and hyperoxia. Hyperoxia-mediated reduction in PVR was first reported by McMahon et al. (44), in human subjects at rest and breathing 100% O₂ at 3 ATA, and was associated with increased erythrocyte S-nitrosohemoglobin levels. The present study demonstrates a reduction in MPAP and PVR with hyperoxia during exercise, compared with normoxia at the same depth and similar gas density. In normoxia, MPAP was higher at depth compared with surface, an effect that was abolished by hyperoxia. Acidemia induces pulmonary vasoconstriction; however, arterial pH did not differ between normoxia at depth and surface or between hyperoxia and normoxia at depth. This suggests that the differences seen in MPAP occurred because of another mechanism. Higher CO and PaCO₂ are the most likely mechanisms for increased MPAP at depth compared with surface. During hyperoxia at depth, MPAP and PVR were reduced compared with normoxia at depth despite significantly

higher PaCO₂ and similar CO. These findings are consistent with an effect of O₂-mediated pulmonary vasodilatation.

We cannot exclude the possibility that the slightly higher MPAP during normoxia at depth might have been due to effects of alterations in lung volume and intrathoracic pressure. If higher gas density and individual breathing strategy in response to greater airway resistance at depth resulted in a net positive mean intrathoracic pressure averaged over the respiratory cycle, then this would cause a rise in transduced pulmonary artery pressure. Such an effect, if present, could obscure subtle changes in transmural pulmonary artery pressures at depth. Additionally, there may be some effect of increased sympathetic tone at depth as a result of increased WOB with higher gas density and inspiratory muscle fatigue (61). Because acid-base status did not change from early to late exercise, an effect of progressive acidosis on MPAP during underwater exercise could not be demonstrated in this study.

Implications for immersion pulmonary edema. MPAP varied widely between individuals (up to a 2- to 3-fold difference among subjects), which may provide an explanation for the differential susceptibility to IPE among individuals. There were measurements of MPAP during submaximal exercise that rose above the threshold for pathological pulmonary artery pressures (MPAP >30 mmHg with exercise), which could represent those individuals susceptible to IPE. This finding is in contrast to dry exercise, in which such high values are only observed during maximal exercise (33). We did not see major blood gas changes, nor did pulmonary vascular pressures increase over the course of 16 min of exercise. Our findings suggest that at a given level of exertion, the risk of developing IPE is greater at depth than at the surface, but that this risk is reduced by high PO₂.

PA_{O2}-Pa_{O2} difference. In normoxia, PA_{O2}-Pa_{O2} difference was similar at the surface and at depth. Other studies have shown an inverse relationship at rest between gas density and PA_{O2}-Pa_{O2} difference, possibly as a result of improved \dot{V}_A/\dot{Q} matching (17, 19, 57, 68). In contrast to these previous studies, the present study combined exercise, immersion, and prone positioning, each of which has the effect of increasing pulmonary blood flow. In presence of hypoventilated lung regions, increased \dot{Q} could worsen \dot{V}_A/\dot{Q} mismatching. This may offset any improvement in \dot{V}_A/\dot{Q} matching effected by increased gas density and convective mixing (47, 68).

In the present study, during normoxic exercise at both surface and depth, PA_{O2}-Pa_{O2} difference increased from early to late exercise, consistent with the PA_{O2}-Pa_{O2} difference patterns seen in dry exercise (25). In the dry, multiple-inert gas elimination analysis has shown a pattern consistent with interstitial pulmonary edema in athletes during prolonged, heavy exercise in the dry (25). Although lung water was not measured in this study, an increase in PA_{O2}-Pa_{O2} difference over the course of the exercise period is consistent with early interstitial pulmonary edema.

Limitations. Because of risks associated with performing moderately heavy exertion shortly after decompression, studies at depth were always performed after studies at the surface. We therefore cannot exclude potential effects of exercise on hemodynamic and respiratory parameters measured at depth.

In the present study, we did not use a negative P_{tr} as in the studies by Wylegala et al. (69) and Ray et al. (53, 54), although we did see a similar increase in \dot{V}_E at the surface. Although in

our study workload was adjusted to individual exercise capacity to some degree, there was possibly greater heterogeneity of response than if we had specified a work rate at a fixed fraction of $\dot{V}_{O_{2max}}$.

Summary. To our knowledge, this the first study to investigate respiratory parameters and pulmonary hemodynamics during prolonged, immersed exercise with of range of Pi_{O_2} of 0.2–1.75 ATA. During 16 min of prone underwater exercise, \dot{V}_E increased at the surface but not at 4.7 ATA. Progressive acidosis did not occur. In healthy subjects, a worsening of metabolic acidosis as a cause for hyperventilation is not supported by findings of this study. The results are consistent with respiratory muscle fatigue as a cause of the increase in \dot{V}_E . Ventilation was reduced by depth and further reduced by hyperoxia at depth. MPAP in underwater exercise increased with the onset of exercise, and tended to decrease as exercise continued, an effect that was significant only at the surface. There was a two- to threefold variation among the 10 subjects in MPAP and PAWP, consistent with variation in individual susceptibility to IPE. Pulmonary vascular pressures were elevated by exercise compared with rest at all depth and Pi_{O_2} conditions. The elevated pulmonary vascular pressures during exercise were accompanied by an increase in $P_{A_{O_2}}-P_{a_{O_2}}$ difference from early to late exercise, which suggests an increase in lung water. We cannot exclude the possibility that respiratory muscle failure might have been induced by increased respiratory load during submersed exercise and possibly local acid accumulation in respiratory muscle (69).

ACKNOWLEDGMENTS

The authors are grateful to Eric Alford for his technical assistance with gas chromatography.

GRANTS

This study was supported by Naval Sea Systems Command (NAVSEA) Contract N0463A-07-C-0002. D. F. Peacher was supported in part by Duke University's CTSA grant TL1-RR-024126 from NCR/NH.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

REFERENCES

- Adir Y, Shupak A, Gil A, Peled N, Keynan Y, Domachevsky L, Weiler-Ravell D. Swimming-induced pulmonary edema: clinical presentation and serial lung function. *Chest* 126: 394–399, 2004.
- Aliverti A, Bovio D, Fullin I, Dellaca RL, Lo Mauro A, Pedotti A, Macklem PT. The abdominal circulatory pump. *PLoS ONE* 4: 1–15, 2009.
- Anonymous. National Committee for Clinical Laboratory Standards: Definitions of Quantities and Conventions Related to Blood pH and Gas Analysis; Approved Standard. In: *NCCLS Document C12-A*. Villanova, PA: National Committee for Clinical Laboratory Standards, 1994.
- Barratt-Boyes BG, Wood EH. Hemodynamic response of healthy subjects to exercise in the supine position while breathing oxygen. *J Appl Physiol* 11: 129–135, 1957.
- Bidart CM, Abbas AE, Parish JM, Chaliki HP, Moreno CA, Lester SJ. The noninvasive evaluation of exercise-induced changes in pulmonary artery pressure and pulmonary vascular resistance. *J Am Soc Echocardiogr* 20: 270–275, 2007.
- Biswas R, Shibu PK, James CM. Pulmonary oedema precipitated by cold water swimming. *Br J Sports Med* 38: e36, 2004.
- Burnett RW, Noonan DC. Calculations and correction factors used in determination of blood pH and blood gases. *Clin Chem* 20: 1499–1506, 1974.
- Cherry AD, Forkner IF, Frederick HJ, Natoli MJ, Schinazi EA, Longphre JP, Conard JL, White WD, Freiburger JJ, Stolp BW, Pollock NW, Doar PO, Boso AE, Alford EL, Walker AJ, Ma AC, Rhodes MA, Moon RE. Predictors of increased P_{aCO_2} during immersed prone exercise at 4.7 ATA. *J Appl Physiol* 106: 316–325, 2009.
- Cochard G, Arvieux J, Lacour JM, Madouas G, Mongredien H, Arvieux CC. Pulmonary edema in scuba divers: recurrence and fatal outcome. *Undersea Hyperb Med* 32: 39–44, 2005.
- Cohen CA, Zigelbaum G, Gross D, Roussos C, Macklem P. Clinical manifestations of inspiratory muscle fatigue. *Am J Med* 73: 308–316, 1982.
- Craig AB Jr, Dvorak M. Thermal regulation of man exercising during water immersion. *J Appl Physiol* 25: 28–35, 1968.
- Dahlback GO, Jonsson E, Liner MH. Influence of hydrostatic compression of the chest and intrathoracic blood pooling in static lung mechanics during head-out immersion. *Undersea Biomed Res* 5: 71–85, 1978.
- Damato AN, Galante JG, Smith WM. Hemodynamic response to treadmill exercise in normal subjects. *J Appl Physiol* 21: 956–966, 1966.
- Dempsey JA, McKenzie DC, Haverkamp HC, Eldridge MW. Update in the understanding of respiratory limitations to exercise performance in fit, active adults. *Chest* 134: 613–622, 2008.
- Duncker DJ, Stubenitsky R, Tonino PA, Verdouw PD. Nitric oxide contributes to the regulation of vasomotor tone but does not modulate O_2 -consumption in exercising swine. *Cardiovasc Res* 47: 738–748, 2000.
- Ekelund LG, Holmgren A. Circulatory and respiratory adaptation during long-term, non-steady state exercise in the sitting positions. *Acta Physiol Scand* 62: 240–255, 1964.
- Flynn ET, Saltzman HA, Summitt JK. Effects of head-out immersion at 19.18 ATA on pulmonary gas exchange in man. *J Appl Physiol* 33: 113–119, 1972.
- Gelfand R, Lambertsen CJ. Dynamic respiratory response to abrupt change of CO_2 at normal and high PO_2 . *J Appl Physiol* 35: 903–913, 1973.
- Gledhill N, Froese AB, Buick FJ, Bryan AC. VA/Q inhomogeneity and $AaDO_2$ in man during exercise: effect of SF6 breathing. *J Appl Physiol* 45: 512–515, 1978.
- Hampson NB, Dunford RG. Pulmonary edema of scuba divers. *Undersea Hyperb Med* 24: 29–33, 1997.
- Harms CA, Wetter TJ, McClaran SR, Pegelow DF, Nickle GA, Nelson WB, Hanson P, Dempsey JA. Effects of respiratory muscle work on cardiac output and its distribution during maximal exercise. *J Appl Physiol* 85: 609–618, 1998.
- Hatridge J, Haji A, Perez-Padilla JE, Remmers JE. Rapid shallow breathing caused by pulmonary vascular congestion in cats. *J Appl Physiol* 67: 2257–2264, 1989.
- Hayashi K, Honda Y, Ogawa T, Kondo N, Nishiyasu T. Relationship between ventilatory response and body temperature during prolonged submaximal exercise. *J Appl Physiol* 100: 414–420, 2006.
- Higginbotham MB, Morris KG, Williams RS, McHale PA, Coleman RE, Cobb PR. Regulation of stroke volume during submaximal and maximal upright exercise in normal man. *Circ Res* 58: 281–291, 1986.
- Hopkins SR, Gavin TP, Siafakas NM, Haseler LJ, Olfert M, Wagner H, Wagner PD. Effect of prolonged, heavy exercise in pulmonary gas exchange in athletes. *J Appl Physiol* 85: 1523–1532, 1998.
- Hyde RW, Lawson WH, Forster RE. Influence of carbon dioxide on pulmonary vasculature. *J Appl Physiol* 19: 734–744, 1964.
- Jayaweera AR, Ehrlich W. Changes of phasic pleural pressure in awake dogs during exercise: potential effects on cardiac output. *Ann Biomed Eng* 15: 311–318, 1987.
- Johnson BD, Babcock MA, Suman OE, Dempsey JA. Exercise-induced diaphragmatic fatigue in healthy humans. *J Physiol* 460: 385–405, 1993.
- Kajiser L. Limiting factors for aerobic muscle exercise. *Acta Physiol Scand Suppl* 346: 26–58, 1970.
- Kearon MC, Summers E, Jones NL, Campbell EJM, Killiam KJ. Breathing during prolonged exercise in humans. *J Physiol* 442: 477–487, 1991.
- Koehle MS, Lepawsky M, McKenzie DC. Pulmonary oedema of immersion. *Sports Med* 35: 183–190, 2005.
- Koizumi T, Gupta R, Banerjee M, Newman JH. Changes in pulmonary vascular tone during exercise. Effects of nitric oxide (NO) synthase inhibition, L-arginine infusion, and NO inhalation. *J Clin Invest* 94: 2275–2282, 1994.
- Kovacs G, Berghold A, Scheidl S, Olschewski H. Pulmonary arterial pressure during rest and exercise in healthy subjects: a systematic review. *Eur Respir J* 34: 888–894, 2009.
- Kurss DI, Lundgren CEG, Pasche AJ. Effect of water temperature on vital capacity in head-out immersion. In: *Underwater Physiology VII*

- Proceedings of the 7th Symposium on Underwater Physiology*, edited by Bachrach AJ, and Matzen MM. Bethesda, MD: Undersea Med. Soc., 1981, p. 297–301.
35. **Lambertsen CJ, Owen SG, Wendel H, Stroud MW, Lurie AA, Lochner W, Clark GF.** Respiratory and cerebral circulatory control during exercise at 21 and 20 atmospheres inspired pO₂. *J Appl Physiol* 14: 966–982, 1959.
 36. **Lanphier E.** *Nitrogen-Oxygen Mixture Physiology. Phase 4: Carbon Dioxide Sensitivity as a Potential Means of Personnel Selection. Phase 6: Carbon Dioxide Regulation Under Diving Conditions.* Panama City, FL: US Navy Experimental Diving Unit, 1958.
 37. **Linnarsson D, Hesser CM.** Dissociated ventilatory and central respiratory responses to CO₂ at raised N₂ pressure. *J Appl Physiol* 45: 756–761, 1978.
 38. **Ludwig B, Mahon R, Parrish J, Lamb C, Kerr S.** Pulmonary edema in combat swimmers: clinical and bronchoalveolar lavage description demonstrating stress failure of the pulmonary capillaries. *Undersea Hyperb Med* 31: C42, 2004.
 39. **Lund KL, Mahon RT, Tanen DA, Bakhda S.** Swimming-induced pulmonary edema. *Ann Emerg Med* 41: 251–256, 2003.
 40. **MacDonald JR.** Potential causes, mechanisms, and implications of post exercise hypotension. *J Hum Hypertens* 16: 225–236, 2002.
 41. **Mahon RT, Kerr S, Amundson D, Parrish JS.** Immersion pulmonary edema in special forces combat swimmers. *Chest* 122: 383–384, 2002.
 42. **Manohar M, Goetz TE.** L-NAME does not affect exercise-induced pulmonary hypertension in thoroughbred horses. *J Appl Physiol* 84: 1902–1908, 1998.
 43. **Martin BJ, Morgan EJ, Zwillich CW, Weil JV.** Control of breathing during prolonged exercise. *J Appl Physiol* 50: 27–31, 1981.
 44. **McMahon TJ, Moon RE, Luschinger BP, Carraway MS, Stone AE, Stolp BW, Gow AJ, Pawloski JR, Watke P, Singel DJ, Piantadosi CA, Stamler JS.** Nitric oxide in the human respiratory cycle. *Nat Med* 8: 711–717, 2002.
 45. **Merkus D, Houweling B, Zarbanoui A, Duncker DJ.** Interaction between prostanoids and nitric oxide in regulation of systemic, pulmonary, and coronary vascular tone in exercising swine. *Am J Physiol Heart Circ Physiol* 286: H1114–H1123, 2004.
 46. **Miller JD, Smith CA, Hemauer SJ, Dempsey JA.** The effects of inspiratory intrathoracic pressure production on the cardiovascular response to submaximal exercise in health and chronic heart failure. *Am J Physiol Heart Circ Physiol* 292: H580–H592, 2007.
 47. **Moon RE, Cherry AD, Stolp BW, Camporesi EM.** Pulmonary gas exchange in diving. *J Appl Physiol* 106: 668–677, 2009.
 48. **Morrison JB, Florio JT, Butt WS.** Observations after loss of consciousness under water. *Undersea Biomed Res* 5: 179–187, 1978.
 49. **Overend TJ, Cunningham DA, Paterson DH, Smith WDF.** Physiological responses of young and elderly men to prolonged exercise at critical power. *Eur J Appl Physiol* 64: 187–193, 1992.
 50. **Paintal AS.** Mechanism of stimulation of type J pulmonary receptors. *J Physiol* 203: 511–532, 1969.
 51. **Pinsky MR.** Hemodynamic effects of ventilation and ventilatory maneuvers. In: *Respiratory-Circulatory Interactions in Health and Disease*, edited by Scharf SM, Pinsky MR, Magder S. New York: Dekker, 2001, p. 183–218.
 52. **Prefaut C, Lupi-HE, Anthonisen NR.** Human lung mechanics during water immersion. *J Appl Physiol* 40: 320–323, 1976.
 53. **Ray AD, Pendergast DR, Lundgren CEG.** Respiratory muscle training improves swimming endurance at depth. *Undersea Hyperb Med* 35: 185, 2008.
 54. **Ray AD, Pendergast DR, Lundgren CEG.** Respiratory muscle training reduces the work of breathing at depth. *Eur J Appl Physiol* 108: 811–820, 2010.
 55. **Robotham JL, Peters J.** Mechanical effects of intrathoracic pressure on ventricular performance. In: *Heart-Lung Interactions in Health and Disease*, edited by Scharf SM, Cassiday SS. New York: Dekker, 1989, p. 251–283.
 56. **Romer LM, Polkey MI.** Exercise-induced respiratory muscle fatigue: implications for performance. *J Appl Physiol* 104: 879–888, 2008.
 57. **Saltzman HA, Salzano JV, Blenkarn GD, Kylstra JA.** Effects of pressure on ventilation and gas exchange in man. *J Appl Physiol* 30: 443–449, 1971.
 58. **Salzano JV, Camporesi EM, Stolp BW, Moon RE.** Physiological responses to exercise at 47 and 66 ATA. *J Appl Physiol* 57: 1055–1068, 1984.
 59. **Siggaard-Andersen O.** *The Acid-Base Status of the Blood.* Baltimore: Williams and Wilkins, 1974.
 60. **Slonim NB, Ravin A, Balchum OJ, Dressler SH.** The effect of mild exercise in the supine position on the pulmonary arterial pressure of five normal human subjects. *J Clin Invest* 33: 1022–1030, 1954.
 61. **St Croix CM, Morgan BJ, Wetter TJ, Dempsey JA.** Fatiguing inspiratory muscle work causes reflex sympathetic activation in humans. *J Physiol* 529: 493–504, 2000.
 62. **Stanek V, Jebavy P, Hurrych J, Widimsky J.** Central haemodynamics during supine exercise and pulmonary artery occlusion in normal subjects. *Bull Physiopath Respir (Nancy)* 9: 1203–1217, 1973.
 63. **Taylor JFN, Lee JC, Downing SE.** Effects of acidosis, catechols, and atrial function on pulmonary pressure gradients. *J Surg Res* 18: 587–596, 1975.
 64. **Thalmann ED, Sponholtz DK, Lundgren CE.** Chamber-based system for physiological monitoring of submerged exercising subjects. *Undersea Biomed Res* 5: 293–300, 1978.
 65. **Wasserman K, Whipp BJ, Casaburi R.** Respiratory control during exercise. In: *Handbook of Physiology. The Respiratory System. Control of Breathing.* Bethesda, MD: Am Physiol Soc, 1965, sect. 3, vol. II, pt. 2, chapt. 17, p. 595–619.
 66. **Wester TE, Cherry AD, Pollock NW, Freiburger JJ, Natoli MJ, Schinazi EA, Doar PO, Boso AE, Alford EL, Walker AJ, Uguccioni DM, Kernagis D, Moon RE.** Effects of head and body cooling on hemodynamics during immersed prone exercise at 1 ATA. *J Appl Physiol* 106: 691–700, 2008.
 67. **Wilmshurst PT, Crowther A, Nuri M, Webb-Peploe MM.** Cold-induced pulmonary oedema in scuba divers and swimmers and subsequent development of hypertension. *Lancet* 333: 62–65, 1989.
 68. **Wood LD, Bryan AC, Bau SK, Weng TR, Levinson H.** Effect of increased gas density on pulmonary gas exchange in man. *J Appl Physiol* 41: 206–210, 1976.
 69. **Wylegala JA, Pendergast DR, Gosselin LE, Warkander DE, Lundgren CEG.** Respiratory muscle training improves swimming endurance in divers. *Eur J Appl Physiol* 99: 393–404, 2007.